

TETRACYCLINE was discounted for ITEM-1 because there is evidence that this e.coli is not sensitive to it.

Would you like to see some details? ** NO

** HOW DO YOU USE THE TYPE OF THE INFECTION?

The following rules use:
the type of the infection

154, 578, 574, 572, 570, 565, 564, 559, 557, 553, 551, 549, 547, 545, 543, 541,
539, 537, 535, 533, 531, 529, 523, 520, 519, 517, 515, 513, 511, 507, 300,
289, 288, 287, 280, 174, 167

The parameter most frequently concluded by these rules is:
the organisms (other than those seen on cultures or smears) which might
be causing the infection

Would you like a summary of ALL the parameters concluded by these rules?

** NO

Which of the rules do you wish to see?

** 280

RULE280

[This rule applies to all cultures, and is tried in order to find out about
the organisms (other than those seen on cultures or smears) which might
be causing the infection]

- If:
- 1) The infection which requires therapy is meningitis, and
 - 2) The type of the infection is fungal, and
 - 3) Organisms were not seen on the stain of the culture, and
 - 4) The patient is not a compromised host, and
 - 5) The patient has been to an area that is endemic for coccidiomycoses,
and
 - 6) The race of the patient is one of: black asian indian, and
 - 7) The cryptococcal antigen in the csf was not positive

Then: There is suggestive evidence (.5) that cryptococcus is not one of the
organisms (other than those seen on cultures or smears) which
might be causing the infection

Author: YU

Justification: Dark-skinned races, especially Filipino, Asian, and Black (in
that order) have an increased susceptibility to coccidiomycoses
meningitis.

Literature: Stevens, D.A. et al. Miconazole in Coccidiomycosis. Am J Med,
60:191-202, Feb 1976.

** HOW DO YOU TREAT PNEUMOCOCCAL PNEUMONIA

The MYCIN system currently can treat the following infections: BACTEREMIA
MENINGITIS CYSTITIS. Because the knowledge base is incomplete, all other
infections will be treated like bacteremia.

For treatment of DIPLOCOCCUS-PNEUMONIAE in BACTEREMIA

The drugs of choice (ranked by relative efficacy, assuming sensitivity) are:

1st choice:

PENICILLIN

AMPICILLIN

2nd choice:

NAFCILLIN

CEPHALOTHIN

ERYTHROMYCIN

CLINDAMYCIN

3rd choice:

TETRACYCLINE

CHLORAMPHENICOL

VANCOMYCIN

Duration of therapy: 28 days

**** WHAT DOSE OF ERYTHROMYCIN DO YOU RECOMMEND?**

When ERYTHROMYCIN is given for BACTEREMIA, the recommended dosage is:

if age is > 12 yrs then 12 mg/kg q6h IV

else if age is > .08 yrs then 5 mg/kg q6h IV

else if age is > .02 yrs then 5 mg/kg q12h IV

[Different dosages are recommended for different infections.]

**** HOW DO YOU TREAT CYSTITIS**

In general, treatment for an infection depends on the causative organism.

Please include in your question the organism of interest.

**** STOP**

VI. Dose Calculation Consultation Session

MYCIN 3-Jun-78 ...

Special options (type ? for help):

** DOSE

Instructions? (Y or N)

** YES

This program makes dosage recommendations for a patient with an infectious disease. You will be asked a few facts about the patient which will be used to determine the appropriate dosages. Since the recommended dose of an antibiotic may differ with infection, you will first be asked to enter the infection for which the drugs are to be given. Then you will be prompted for an antibiotic and will be told what dosage to give. You may then request dosing information for another antibiotic (type RETURN if you are not interested in other drugs). You may also request dosing information for antibiotics to treat another infection (type RETURN when you are done).

-----PATIENT-541-----

1) Patient's name:

** OSCAR LOVEJOY

2) Age:

** 34

3) Sex:

** M

4) Do you have reason to suspect that Oscar Lovejoy may have impaired renal function?

** Y

5) What is the most recent creatinine clearance in ml/min which you feel is a true representation of Oscar Lovejoy's renal function?

** U

6) What is the most recent serum creatinine of Oscar Lovejoy (in mg/100ml)?

** 1.9

7) What is the previous serum creatinine of Oscar Lovejoy (in mg/100ml)?

** 1.8

8) Number of days between Oscar Lovejoy's two most recent serum creatinines:

** 2

9) Oscar Lovejoy's weight in kilograms (or <number> POUNDS):

** 70

10) Oscar Lovejoy's height in centimeters (or <number> INCHES):

** 175

Estimated body surface area is 1.9 sq. meters.

Dosage adjustments will be based on the calculated creatinine clearance of 42.7 ml/min/1.73 sq. meters (adjusted to average body surface area.)

Infection: MENINGITIS

Drug: GENTAMICIN

After a loading dose of:

112 mg (2.8 ml, 80mg/2ml ampule) IV [calculated on basis of 1.6 mg/kg],

give:

70 mg (1.8 ml, 80mg/2ml ampule) q8h IV [calculated on basis of 1.0 mg/kg] plus consider giving 5 mg q24h Intrathecal

Or, after a loading dose of:

140 mg (3.6 ml, 80mg/2ml ampule) IV [calculated on basis of 2.0 mg/kg],

give:

119 mg (3.0 ml, 80mg/2ml ampule) q14h IV [calculated on basis of 1.7 mg/kg] plus consider giving 5 mg q24h Intrathecal

[normal dose is (1.7 mg/kg q8h IV plus consider giving 5 mg q24h Intrathecal)]

New interval (or CR)

** 12

After a loading dose of:

133 mg (3.4 ml, 80mg/2ml ampule) IV [calculated on basis of 1.9 mg/kg],

give:

105 mg (2.6 ml, 80mg/2ml ampule) q12h IV [calculated on basis of 1.5 mg/kg] plus consider giving 5 mg q24h Intrathecal

Drug: CHLORAMPHENICOL

Give: 1.75g (17.6 ml) q6h IV [calculated on basis of 25 mg/kg]

Drug:

Infection:

Please ask any simple-English questions regarding the above consultation session or the overall knowledge of the consultation system. When discussing the consultation above, please refer to organisms, cultures, etc. by their numeric names (eg. ORGANISM-1). Questions which were asked during the consultation may be specified by the numbers that preceded them above, (e.g., 'WHY DID YOU ASK QUESTION 1?'). Control-O will abort type-out, or 'cancel' the current question. Type HELP for a list of the options available. Enter the word STOP when you have no further questions.

Type HELP for the list of question options.

** JUSTIFICATION

** LITERATURE

** HOW DID YOU CALCULATE THE DOSE FOR GENTAMICIN?

When GENTAMICIN is given for MENINGITIS, the recommended dosage is:
if age is > 2 yrs then 1.7 mg/kg q8h IV plus consider giving 5 mg q24h Intrathecal
else 2.3 mg/kg q8h IV plus consider giving 2.5-4 mg/day intrathecal

The normal dose for Oscar Lovejoy is: 119 mg (3.0 ml, 80mg/2ml ampule) q8h IV [calculated on basis of 1.7 mg/kg] plus consider giving 5 mg q24h Intrathecal.

GENTAMICIN is excreted by the kidneys, so its dosage must be modified in renal failure.

The following table shows how the patient's renal function was determined:

Identifier	Value	Definition
SCR1	1.9	the most recent serum creatinine of oscar lovejoy (in mg/100ml)
SCR2	1.8	the previous serum creatinine of oscar lovejoy (in mg/100ml)
CCR	46.9	oscar lovejoy's most recent creatinine clearance (in ml/min)
CCr(f)	42.7	oscar lovejoy's creatinine clearance, adjusted for normal body surface area (ml/min/1.73 sq. meters)
CCr(n)	100	the average normal creatinine clearance for oscar lovejoy's age group
CCr(min)	80	the minimum normal creatinine clearance for oscar lovejoy's age group

Since $CCr(f) < CCr(min)$, PATIENT-541 has renal impairment.

To modify the dosage of GENTAMICIN, the following pharmacokinetic parameters were used:

Identifier	Value	Definition
a	7.0	the percentage hourly loss of a drug due to nonrenal processes
b	.22	the slope of the plot of the elimination rate constant of a drug versus the patient's creatinine clearance
Q	.57	the drug's elimination rate fraction: elimination rate of the drug as a fraction of the drug's 'normal' elimination rate.

Q was calculated using the formula:

$$Q = [a + b * CCr(f)] / [a + b * CCr(n)]$$

My first dosage recommendation decreased the amount of GENTAMICIN and left the dosing interval unchanged. The new amount was calculated by multiplying the old amount by Q.

The second recommendation increased the dosing interval and left the amount of GENTAMICIN unchanged. The new interval was calculated by dividing the old interval by Q.

** HOW DID YOU DETERMINE THE PATIENT'S BODY SURFACE AREA?

RULE104 was used to conclude that oscar lovejoy's estimated body surface area

is 1.9. The last question asked before the conclusion was made was 10.

** PR 104

RULE104

[This rule applies to any patient, and is tried in order to find out about the patient's estimated body surface area]

If: 1) The weight of the patient is known, and
2) The height of the patient is known

Then: Use Boyd's algorithm to calculate body surface area from weight and height [Boyd, E. The Growth of the Surface Area of the Human Body, 1935 pp 1 - 133.]

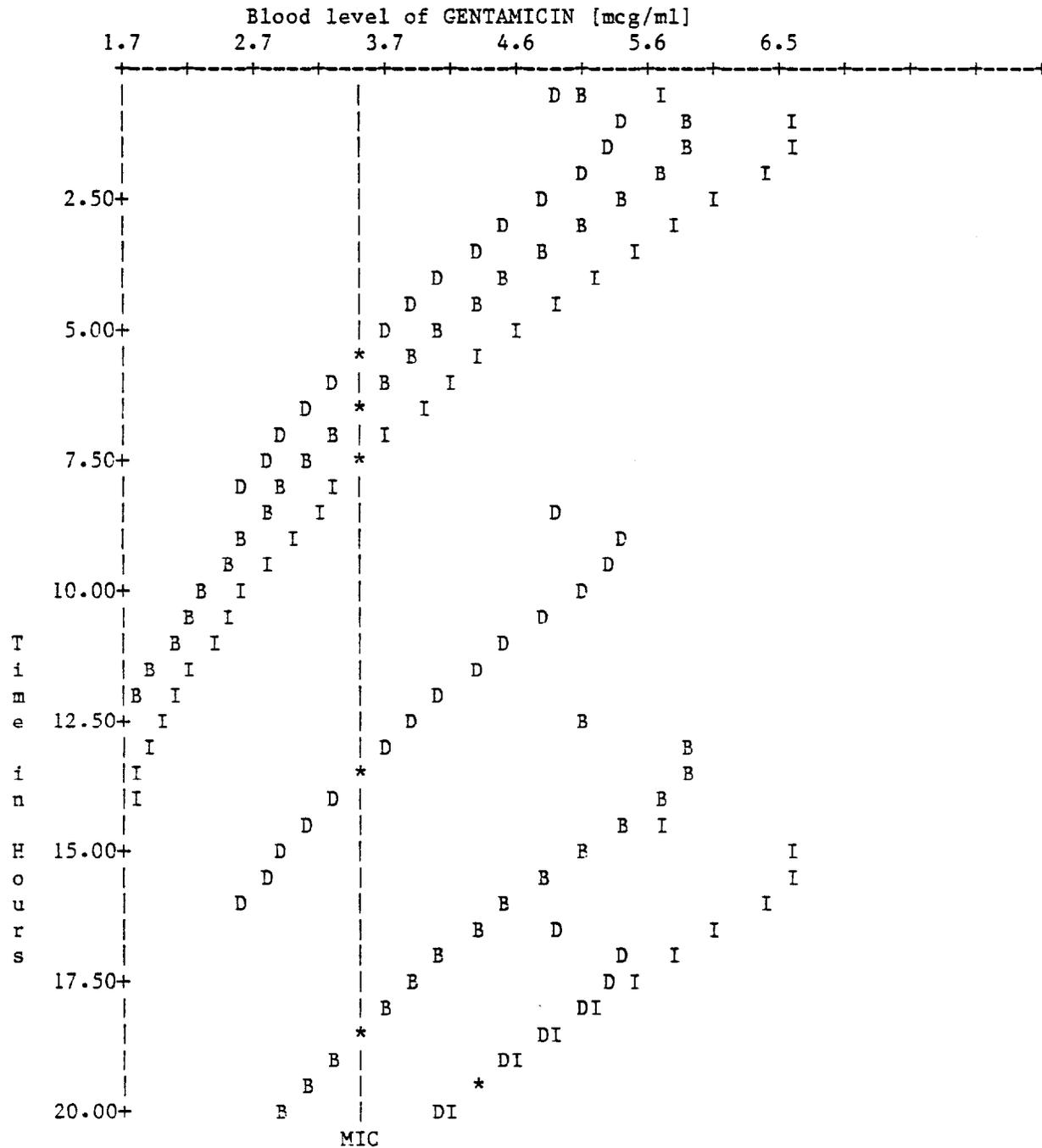
Author: Wraith

Justification: A comparative evaluation with statistical analysis of the Boyd method with the DuBois formula demonstrated that the Boyd formula is more accurate for abnormal body types. [Sendray J et.al., Determination of human body surface area from height and weight, Applied Physiology, 7(1):1-12, July 1954.]

Literature: Boyd, E, The growth of the surface area of the human body, c. 1935, pp 1-133.

VII. Graph of Blood Levels of Anitbiotics

The graph below provides an estimate of the steady state blood levels of gentamicin over time for the three regimens suggested by Mycin. A graph of this form may aid the physician in the selection of the most appropriate regimen.



KEY

D - drug level for modified dose [70.0 mgm every 8.0 hours]

- I - drug level for modified interval [119.0 mgm every 14.0 hours]
- B - drug level for modified interval and dose [98.0 mgm every 12.0 hours]
- MIC - minimum inhibitory concentration [mcg/ml]
- TL - toxic level [mcg/ml]
- * - indicates overlapping curves

VII. Therapy Recommendation Consultation Session

MYCIN 3-Jun-78 ...

Special options (type ? for help):
 ** REC

Instructions? (Y or N)
 ** YES

This program recommends therapy for a patient with infectious diseases. You will be asked a few facts about the patient which will be used to determine the dosages and appropriateness of giving certain antibiotics. Then you will be prompted for the infection(s) that you want treated and the organism(s) which you feel may be responsible for each infection.

MYCIN cannot make a recommendation without knowing the infection(s) and organism(s) to be treated. Other information is requested for the purpose of refining therapy selection, but is not essential; you may answer UNKNOWN to any of these questions.

Case 2, AA, 47-24-31, VMC, A 3 year old female with one day history of headache, lethargy, fever to 104. L.P.: Protein 25, glucose 95 110 cells with 96% polys. Pe: Meningismus, petechiae on arms and shoulders.

28-NOV-77 11:05:51
 [consultation of 23-JUN-76 12:00]

-----PATIENT-683-----

- 1) Patient's name: (first-last)
 ** PT683
- 2) Age:
 ** 3.5
- 3) Sex:
 ** FEMALE
- 4) Is Pt683 currently receiving therapy with any antimicrobial agent?
 ** NO
- 5) During the present illness, has Pt683 been treated with an antimicrobial agent which is no longer being administered?
 ** NO

Infection: MENINGITIS

Organism: VIRUS

[Determining which drugs are desirable for use against the Virus...]

Are there any other organisms which might be causing this meningitis?

** YES

Organism: HEMOPHILUS-INFLUENZAE

- 6) Has the lab reported the in-vitro antibiotic sensitivities of the hemophilus-influenzae causing the meningitis (ITEM-2)?

** N

[Determining which drugs are desirable for use against the Hemophilus-influenzae...]

- 7) Does Pt683 have a clinically significant allergic reaction to any antimicrobial agent?

** NO

Are there any other organisms which might be causing this meningitis?

** YES

Organism: NEISSERIA-MENINGITIDIS

8) Has the lab reported the in-vitro antibiotic sensitivities of the neisseria-meningitidis causing the meningitis (ITEM-3)?

** N

[Determining which drugs are desirable for use against the Neisseria-meningitidis...]

Are there any other organisms which might be causing this meningitis?

** NO

Are there additional infections for which you want therapy recommendations?

** NO

INFECTION-1 is MENINGITIS

+ ... VIRUS Supportive therapy.
 + <ITEM-2> HEMOPHILUS-INFLUENZAE
 + <ITEM-3> NEISSERIA-MENINGITIDIS

[Considering AMPICILLIN-AND-CHLORAMPHENICOL for use against INFECTION-1...]

9) What is the most recent creatinine clearance in ml/min which you feel is a true representation of Pt683's renal function?

** UNKNOWN

10) What is the most recent serum creatinine of Pt683 (in mg/100ml)?

** UNKNOWN

11) Pt683's weight in kilograms (or <number> POUNDS):

** 17.7

[REC-1] My preferred therapy recommendation is as follows:

In order to cover for Items <2 3>:

Give the following in combination:

1) AMPICILLIN

Dose: 886 mg (7.0 ml) q4h IV [calculated on basis of 50 mg/kg]

[The dose should be modified in SEVERE renal failure. I can adjust the dose only if a creatinine clearance or a serum creatinine is obtained, and the patient's weight is known.]

2) CHLORAMPHENICOL

Dose: 443 mg (4.4 ml) q6h IV [calculated on basis of 25 mg/kg]

Please ask any simple-English questions regarding the above consultation session or the overall knowledge of the consultation system. When discussing the consultation above, please refer to organisms, cultures, etc. by their numeric names (eg. ORGANISM-1). Questions which were asked during the consultation may be specified by the numbers that preceded them above, (e.g., 'WHY DID YOU ASK QUESTION 1?'). Control-O will abort type-out, or 'cancel' the current question. Type HELP for a list of the options available. Enter the word STOP when you have no further questions.

Type HELP for the list of question options.

**** JUSTIFICATION****** LITERATURE****** WHY DID YOU GIVE AMPICILLIN AND CHLORAMPHENICOL IN REC-1?**

Shall I describe the therapy algorithm for you?**** NO**

AMPICILLIN-AND-CHLORAMPHENICOL was not prescribed for ITEM-1 or ITEM-3
 For ITEM-1 no drug was prescribed.
 For ITEM-3 AMPICILLIN was prescribed.
 AMPICILLIN-AND-CHLORAMPHENICOL was prescribed for ITEM-2 in RECOMMENDATION-1
 because:

- AMPICILLIN-AND-CHLORAMPHENICOL is used for treating hemophilus-influenzae in meningitis
- AMPICILLIN-AND-CHLORAMPHENICOL was considered for treating ITEM-2 because it is more appropriate than AMPICILLIN for this patient. [RULE066]
- ITEM-2 is sensitive to AMPICILLIN-AND-CHLORAMPHENICOL
- there were no contraindications for it
- it was part of the recommendation which covers for all of the items, using the fewest number of drugs.

Would you like to see some details?**** YES**

The following decision(s) are relevant:

The drugs considered for the hemophilus-influenzae ranked according to desirability are ampicillin-and-chloramphenicol (.95) chloramphenicol (.89) carbenicillin (.79) tetracycline (.76) erythromycin (.75) cephalothin (.7) [RULE101 RULE066]

The drugs to which the hemophilus-influenzae is sensitive are ampicillin-and-chloramphenicol (1.0) chloramphenicol (1.0) carbenicillin (1.0) tetracycline (1.0) erythromycin (1.0) cephalothin (1.0) [RULE098 RULE445]
 For the conclusion concerning ampicillin-and-chloramphenicol see RULE445.

The meningitis is one of the infections for which ampicillin-and-chloramphenicol is appropriate [RULE441]

**** PR 66**

RULE066

- If: 1) Ampicillin is one of the drugs considered for the item ranked according to desirability, and
 2) The diagnosis of the infection is meningitis, and
 3) The age of the patient is greater than or equal to 1 week, and
 4) The identity corresponding to the item is hemophilus-influenzae, and
 5) The item is one of the most likely (top cluster) identities causing an infection in the patient, and
 6) It is not known whether ampicillin is one of the drugs to which the item is sensitive in vitro, and
 7) A: The patient is not allergic to one or more antibiotics, or
 B: Chloramphenicol is not one of the drugs to which the patient is allergic

Then: It is definite (1.0) that the combination of ampicillin with chloramphenicol is a more appropriate therapy for use against the item

Author: Wraith

Justification: Due to the increasing number of Ampicillin-resistant Hemophilus influenzae isolated in the last few years a combination of ampicillin and chloramphenicol is recommended until sensitivities of the organism are known. At that time, chloramphenicol should be discontinued unless the organism is ampicillin-resistant, in which case, ampicillin is discontinued.

Literature: 1. Katz SL: Ampicillin-resistant Hemophilus influenzae type B: A status report. *Pediat.* 55:66, 1975.

2. Katz SL et.al.: Ampicillin-resistant strains of Hemophilus influenzae type b, *Pediat.* 55:145, 1975.

3. Nelson JD: Should ampicillin be abandoned for treatment of Hemophilus influenzae disease? *JAMA* 229:322, 1974.

** REC

For each item in turn, enter the drug you would have prescribed in RECOMMENDATION-1.

In order to minimize the number of drugs in your recommendation, you may not want to prescribe therapy for every item. Items which represent the most likely organisms are indicated with a plus sign (+).

+ ITEM-1 -- the virus **
 + ITEM-2 -- the hemophilus-influenzae ** CARBENICILLIN
 + ITEM-3 -- the neisseria-meningitidis ** CARBENICILLIN

[Checking for contraindications...]

[Considering CARBENICILLIN for use against INFECTION-1...]

[No contraindications found...]

[Now comparing your prescription to MYCIN's...]

ORGANISMS	MYCIN's regimen	Your regimen
"most likely"	Drug -- Choice Ranking	Drug -- Choice Ranking
ITEM-2	AMPICILLIN-AND-CHLORAMPHENICOL -- 1st	CARBENICILLIN -- 3rd
ITEM-3	AMPICILLIN -- 1st	CARBENICILLIN -- 2nd

(The desirability of a drug is defined to be its lowest ranking for the items it covers.)

Your recommendation for the most likely organisms(s) is not optimal, since your prescription of 1 third choice drug (CARBENICILLIN for ITEM-3 and ITEM-2) should be avoided.

[You may refer to your regimen as RECOMMENDATION-2 in later questions.]

**** STOP**

IX. Running a Consultation of a Stored Patient in Summary Form
with Rule Acquisition to Correct Diagnosis

Case 10, TS, VMC, 9-49-13-77, A 73 year old female with rheumatoid arthritis, congestive heart failure, and gastritis on chronic prednisone 15 mg/day and coumadin. Admitted for a GI bleed. Progressive obtundation began while in hospital. LP revealed: protein 158, glucose 20, 38 cells with 34 % polys, 66% lymphs. Gram stain and India Ink prep revealed budding yeast-like cells. Treatment: Begun on Amphotericin B IV and IT as well as 5-fc. Final dx: Cryptococcal meningitis.

29-NOV-77 01:45:12
[consultation of 9-OCT-76 12:00]

Pt709 is a 73 year old female, caucasian.
Patient-709 is not an alcoholic.
Patient-709 is a compromised host.
Patient-709 is immunosuppressed.
Patient-709 does not live in a crowded environment.

Past Medical History:

Patient-709 is not allergic to one or more antibiotics.
Patient-709 has not undergone surgery.
Patient-709 does not have a tb risk factor.
Patient-709 has not recently been exposed to a contagious disease.

Recent Medical History:

The csf has not been tested for cryptococcus antigen.
Patient-709 has not shown symptoms of mumps.
Otitis-media is not one of the diagnoses which are consistent with the patient's clinical history.
Epiglottitis is not one of the diagnoses which are consistent with the patient's clinical history.
Patient-709 has not had an injury or insult to, or defect in the CNS.
Patient-709 has had recent neurologic signs.
The duration of the neurological signs is 4 days.
Patient-709 has had recent neurologic symptoms.
The duration of the neurological symptoms is 2 days.

Physical:

The weight of PATIENT-709 is 68.1 kgms.
The height of PATIENT-709 is 165.1 cms.
Patient-709 is febrile.
Patient-709 has not been seriously burned.
Patient-709 does not have a rash or cutaneous lesions.
Patient-709 has not focal neurological signs.
Patient-709 does not have evidence of ocular nerve dysfunction.
Patient-709's X-ray is abnormal.
Active-tb is not one of the diseases which the patient's chest X-ray suggests.
Lobar-pneumonia is not one of the diseases which the patient's chest X-ray suggests.

CULTURE-1: This pending csf culture was drawn on 9-OCT-76 12:00.
A smear of this pending csf culture was examined.

-----ORGANISM-1-----

The stain of ORGANISM-1 is indiaink.

The CSF cultures will be considered to be associated with MENINGITIS.

The number of days since clinical evidence of the infection was first noted is 4 days.

[Considering organisms (other than those isolated from cultures) which might be present...]

Lymphoma is not one of the diagnoses of the patient.

Leukemia is not one of the diagnoses of the patient.

The CSF protein is 158.

The WBC from the CSF is 38.

The percent of pmns in the csf is 34.

The csf glucose value is 20.

The simultaneous blood glucose value is 95.

The results of a recent CBC of pt709 are available.

The white count from pt709's peripheral CBC (in thousands) is 9.4.

Pt709 has received corticosteroids just prior to or during this infection.

The infection was acquired while the patient was hospitalized.

I have found evidence (RULE564) that treatment should also cover for VIRUS causing MENINGITIS.

[Determining which drugs are desirable for use against the virus...]

My therapy recommendations will be designed to treat for organisms that are either very likely or, although less likely, would have a significant effect on therapy selection if they were present. It is important to cover for the following probable infection(s) and associated organism(s):

INFECTION-1 is MENINGITIS

+ ... VIRUS [from clinical evidence only] Supportive therapy.

Please repeat the LP in 8 - 24 hours for cultures (bacterial, fungal, Tb, and viral), cells, and chemistries.

Blood cultures should be drawn.

Is this correct?

** NO

I was unable to make any conclusion about the identity of ORGANISM-1

Is that correct?

** NO

Should it have been possible to conclude a value?

** YES

Which one(s)?

** CRYPTOCOCCUS

Let's look at the CRYPTOCOCCUS ...

Do you want to

- 1) track down the problem yourself, or
- 2) allow me to guide the debugging, or
- 3) ignore it for now and fix it another time?

Type 1, 2 or 3

** 2

The following applicable rule(s) were unable to conclude about whether the identity of ORGANISM-1 is cryptococcus

RULE378

- If: 1) The infection which requires therapy is meningitis, and
 2) The stain of the organism is acidfast
- Then: 1) There is suggestive evidence (.7) that the identity of the organism is mycobacterium-tb, and
 2) There is evidence that the organisms (other than those seen on cultures or smears) which might be causing the infection is coccidioides (-.8) cryptococcus (-.8)

Clause 2 of RULE378 [the stain of the organism is acidfast] was already known to be false for ORGANISM-1, so the rule was never tried.

Is this rule correct?

** YES

Should its premise have succeeded for this case?

** NO

Is there a rule missing?

** YES

Ok, then I need a rule that would allow me to deduce that the identity of ORGANISM-1 is cryptococcus

Would you like to give me such a rule now?

** YES

Good...

The new rule will be called RULE260

- If: 1 - THE INFECTION WHICH REQUIRES THERAPY IS MENINGITIS
 and 2 - THE STAIN IS INDIAINK
 and 3 -

- Then: 1 - THE IDENTITY IS CRYPTOCOCCUS (.7)
 and 2 -

This may take a few moments.

This is my understanding of your rule:

RULE260

- If: 1) The infection which requires therapy is meningitis, and
 2) The stain of the organism is indiaink
- Then: There is suggestive evidence (.7) that the identity of the organism is cryptococcus

Okay? (Yes or No)

** YES

This rule may be best described as a rule which:

- 1 - applies to all organisms
 - 2 - applies to organisms from positive cultures
 - 3 - applies to organisms seen on smears of specimens for pending cultures
- ** 1

Please type your last name- BENNETT

Please describe briefly why you added (or changed) this rule.

Type control-Z when done.

** THE SYSTEM FAILED TO CONCLUDE CRYPTOCOCCUS FOR AN INDIANK STAIN AND
 ** MENINGITIS AS THE INFECTION
 **

RULE260 has now been added to the knowledge base.

I will now re-run the consultation to check the effectiveness of your new rule. Get comfortable, this may take a few moments.

29-NOV-77 01:53:52
 [consultation of 9-OCT-76 12:00]

-----PATIENT-709-----

-----CULTURE-1-----

-----ORGANISM-1-----

The CSF cultures will be considered to be associated with MENINGITIS.
 [Considering organisms (other than those isolated from cultures) which might be present...]

I have found evidence (RULE564) that treatment should also cover for VIRUS causing MENINGITIS.
 [Determining which drugs are desirable for use against the cryptococcus...]
 [Determining which drugs are desirable for use against the virus...]

My therapy recommendations will be designed to treat for organisms that are either very likely or, although less likely, would have a significant effect on therapy selection if they were present. It is important to cover for the following probable infection(s) and associated organism(s):

INFECTION-1 is MENINGITIS

- + <ITEM-1> CRYPTOCOCCUS [ORGANISM-1]
- ... VIRUS [from clinical evidence only] Supportive therapy.

[My recommendations will cover for all of the most likely items (indicated by a "+" above). Less likely items will be covered unless this would

require an excessive number of drugs.]

Well, it appears that things are straightened out.

Is this correct now?

** YES

Good, then the problem's been fixed.

...continuing with therapy selection now.

[Considering 5-FLUOROCYTOSINE-AND-AMPHOTERICIN-B for use against INFECTION-1...]

Estimated body surface area is 1.8 sq. meters.

Dosage adjustments will be based on the calculated creatinine clearance of 85.4 ml/min/1.73 sq. meters (adjusted to average body surface area.)

Normal doses of all drugs will be given

[REC-1] My preferred therapy recommendation is as follows:

Give the following in combination:

1) 5-FLUOROCYTOSINE

Dose: 2.56g (10 250mg-capsules) q6h PO [calculated on basis of 37.5 mg/kg]

Comments: Gradually increase dose from 12 mg/kg q6h to the above dose as tolerated.

2) AMPHOTERICIN-B

Dose: 20 mg (200.0 ml) q24h IV [calculated on basis of .3 mg/kg]

Comments: Begin with 1 mg IV on day 1, 5 mg on day 2, 10 mg on day 3, and then gradually increase dose by 5-10 mg/day until the above dose is administered. Infuse slowly over 3-6 hrs. Plus, consider giving 0.5mg intrathecally every other day. Greater than 15 mg intrathecally is rarely indicated.

Please obtain samples for fungal, TB, and viral cultures, cytology, VDRL (blood and CSF), coccidioides complement-fixation (blood and CSF), cryptococcal antigen (blood and CSF), viral titers (blood and CSF). An infectious disease consult may be advisable.

Blood cultures should be drawn.

APPENDIX B:
KNOWLEDGE ENGINEERING FOR MEDICAL DECISION MAKING:
A Review of Computer-Based Clinical Decision Aids

1 INTRODUCTION

As early as the 1950's it was recognized that computers could conceivably assist with clinical decision making [57], and both physicians and computer scientists began to analyze medical diagnosis with a view to the potential role of automated decision aids in that domain [55]. A variety of techniques have been applied to computer-aided clinical decision making, accounting for at least 800 references in the clinical and computing literature [104]. In this article we review several methodologies and attempt to identify the important issues that account for both the multiplicity of approaches to the problem and the limited clinical success of most of the systems developed to date. Although there have been previous reviews of computer-aided diagnosis [42], [86], [106], our emphasis here will be somewhat different. We will focus on the representation and utilization of knowledge, termed "knowledge engineering," and the inadequacies of data-intensive techniques which have led to the exploration of novel symbolic reasoning approaches during the last decade.

1.1 Reasons For Attempting Computer-Aided Medical Decision Making

It is generally recognized that accelerated growth in medical knowledge has necessitated greater sub-specialization among physicians and more dependence upon assistance from other experts when a patient presents with a complex problem outside one's own area of expertise. The primary care physician who sees the patient initially has thousands of tests available with a wide range of costs (both fiscal and physical) and potential benefits (i.e., arrival at a correct diagnosis or optimal therapeutic management). Even the experts in a field may reach very different decisions regarding the management of a specific case [122]. Diagnoses that are made, and upon which therapeutic decisions are based, have been shown to vary widely in their accuracy [22],[77], [83]. Furthermore, medical decision making has traditionally been learned by medical students in an unstructured way, largely through observing and emulating the thought processes they perceive to be used by their clinical mentors [48].

Thus the motivations for attempts to understand and automate the process of

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clinical decision making have been numerous [106]. They are directed both at diagnostic models and at assisting with patient management decisions. Among the reasons for attempting such work are the following:

(1) To improve the accuracy of clinical diagnosis through approaches that are systematic, complete, and able to utilize data from diverse sources;

(2) To improve the reliability of clinical decisions by avoiding unwarranted influences of similar but not identical cases (a common source of bias among physicians), and by making the criteria for decisions explicit, and hence reproducible;

(3) To make the selection of tests and therapies efficient in that optimal decisions are reached while the expense of time or funds is minimized before definitive action is taken;

(4) To improve our understanding of clinical decision making, both so that future physicians can have better teaching in this area, and so that the computer programs we develop will be more effective and easier to understand by the physicians for whom they are designed.

1.2 The Distinction Between Data And Knowledge

The models on which computer systems base their clinical advice range from data-intensive to knowledge-intensive approaches. If there is a chronology to the field over the last 20 years, it is that there has been progressively less dependence on "pure," observational data and more emphasis on higher-level symbolic knowledge inferred from primary data. We include with domain knowledge a category of "judgmental knowledge" which reflects the experience and opinions of an expert regarding an issue about which the formal data may be fragmentary or nonexistent. Since many decisions made in clinical medicine depend upon this kind of judgmental expertise, it is not surprising that investigators should begin to look for ways to capture and utilize the knowledge of experts in decision making programs. Another reason to move away from purely data-intensive programs is that in medicine the primary data available to decision makers are far from objective [16]. They include subjective reports from patients, and error-prone observations [23]. Also, the terminology used in the reports is not standardized [7] and the classifications often overlap. Thus decision making aids must be knowledgeable about the unreliability of the data as well as the uncertainty of the inference.

For example, data-intensive programs include medical record systems which accumulate large databanks to assist with decision making. There is little knowledge per se in the databank, but there are large amounts of data which can help with decisions and be analyzed to provide new knowledge. A program that retrieves a patient's record for review, or even one that retrieves the records of several patients matching some set of descriptors, is performing a data management task with minimal "knowledge engineering" involved [32], [80]. On the other hand, there is knowledge contained in the conditional probabilities generated from such a databank and utilized for Bayesian analysis. At the other extreme are systems that attempt to understand and utilize the kind of expert knowledge which cannot be easily gleaned from databanks or literature reviews [69], [95]. Systems that model human reasoning or emphasize education of users tend to fall towards this end of the data-knowledge continuum.

We use the term "knowledge engineering", then, to refer to computer-based symbolic reasoning issues such as knowledge representation, acquisition, and explanation [15]. It is along these dimensions that the programs differ most sharply from conventional calculations. For example, these programs can solve problems by pursuing a line of reasoning; the individual inference steps and the whole chain of reasoning may also form the basis for explanations of decisions. A major concern in knowledge engineering is clear separation of the medical knowledge in a program from the inference mechanism that applies that knowledge to individual cases. One goal of this paper is to identify, in the strengths and weaknesses of earlier work, those issues which have motivated several current research groups to investigate the knowledge engineering approach to the automation of clinical decision aids.

1.3 Parameters For Assessing Work In The Field

The barriers to successful implementation of computer-based diagnostic systems have been analyzed on several occasions [7],[19],[99] and these need not be reviewed in detail here. However, in assessing programs it is pertinent to examine several parameters that affect the success and scope of a particular system in light of its intended users and application:

- (1) How accurate is the program?¹

¹Although this is important it is not the only measure of clinical effectiveness. For example, the effects on morbidity, mortality, and length of hospital stay may also be important parameter. As we shall show, few systems have reached a stage of implementation where these parameters could be assessed.

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- (2) What is the nature of the knowledge in the system and how is it generated or acquired?
- (3) How is the clinical knowledge represented, and how does it facilitate the performance goals of the system described?
- (4) How are knowledge and clinical data utilized and how does this impact on system performance?
- (5) Is the system accepted by the users for whom it is intended? Is the interface with the user adequate? Does the system function outside of a research setting and is it suitable for dissemination?
- (6) What is the size of the required computing resource?
- (7) What are the limitations of the approach?

One issue we have chosen not to address is the cost of a system. Not only is information on this question scanty for most of the programs, but expenses generated in a research and development environment do not realistically reflect the costs one would expect from a system once it is operating for service use.

1.4 Overview Of This Paper

An exhaustive review of computer-aided diagnosis will not be attempted in light of the vastness of the field, and we have therefore chosen to review the methodologies by discussing several representative examples of systems that have been described. The seven principal examples we have selected are not necessarily the best nor the most successful; however, they illustrate the issues we wish to discuss and encompass most of the major methodologies that have been applied to computer-based medical decision making. In several cases we have referenced other closely related systems, and the bibliography should therefore guide the reader who wishes to pursue a particular topic more thoroughly. Any attempt to categorize programs in this way is inherently fraught with problems in that several systems appropriately lay claim to more than one methodology. Thus we have occasionally felt obligated to simplify a topic for clarity in light of the overall purposes of this review and the limitations of the space available to us.

Finally, certain kinds of decision making tools have been intentionally deleted from discussion here. These include medical systems that are designed primarily for use by researchers [35], [45], [59], [84]; advanced automated instrumentation techniques such as computerized tomography²; signal processing

²See Kak's article in this issue of the PROCEEDINGS.

techniques such as programs for EKG analysis [73] or patient monitoring [108]; and programs designed largely for data storage and retrieval with the actual analysis and decision making left largely to the clinician [32],[52],[116]. We have also chosen to discuss working computer programs rather than theories suitable for automation or early reports of work in progress.

2 Clinical Algorithms and Automation

2.1 Overview

Clinical algorithms, or protocols, are structured decision making flowcharts to which a diagnostician or therapist can refer when deciding how to manage a patient with a specific clinical problem [90]. In general these algorithms have been designed by expert physicians for use by physicians' assistants or nurse practitioners who are substituting for physicians in the performance of certain routine clinical-care tasks³. The methodology has been developed in part because of a desire to define basic medical logic concisely so that detailed training in pathophysiology would not be necessary for ancillary practitioners. Experience has shown that intelligent high school graduates, selected in large part because of poise and warmth of personality, can provide excellent care guided by protocols after only 4-8 weeks of training. This care has been shown to be equivalent to that given by physicians for the same limited problems, and to be accepted by physicians and patients alike for such diverse clinical situations as diabetes management [51], [60], pharyngitis [34], headache [33], and other disease categories [97], [103].

The role of the computer in such applications has been limited, however. In fact, several groups initially experimented with computer representation of the algorithms but have since abandoned the efforts and resorted to prepared paper forms [51], [103]. In these cases the computer had originally guided the physician assistant's collection of data and had specified precisely what decisions should be made or actions taken, in accordance with the clinical algorithm. However, since the algorithmic logic is generally simple, and can often be represented on a single sheet of paper, the advantages of an automated approach over a manual system have not been clearly demonstrated. In one study

³Clinical algorithms have also been prepared for use by physicians themselves, but Grimm has found that they are generally less well-accepted by doctors [34]. He showed, however, that physician performance could improve when protocols were used in certain settings.

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Vickery showed that, although the computer system entirely eliminated errors in data collection (since the program demanded all relevant data at the appropriate time), supervising physicians could detect no significant difference between the performance of physicians' assistants using automated versus manual systems [103]. Furthermore, the computer could not, of course, decide whether the actual observations entered by the physicians' assistant were correct; yet this kind of inaccuracy was one of the most common reasons that supervisors occasionally found an assistant's performance unsatisfactory.

There are two other ways in which the computer has been utilized in the setting of clinical algorithms. One has been in the use of mathematical techniques to analyze signs and symptoms of diseases and thereby to identify those that should most appropriately be referenced in a clinical algorithm that is being prepared for the management of that disease [26],[50],[105]. The process for distilling expert knowledge in the form of a clinical algorithm can be an arduous and imperfect one [90]; formal techniques to assist with this task may prove to be very valuable.

Finally, some researchers in this area continue to use computers to assist with audit of performance by comparing actual actions taken by a physicians' assistant with those recommended by the algorithm itself. Sox et al. [97] have described a system in which the assistant's checklist for a patient encounter was sent to a central computer and analyzed for evidence of deviation from the accepted protocol. Computer-generated reports then served as feedback to the physicians' assistant and to the supervising physician.

2.2 Example

We have selected for discussion a project that differs from those previously cited in that (1) computer techniques are still being utilized, and (2) the clinical algorithms are designed for use by primary care physicians themselves. This is the cancer chemotherapy system developed in Alabama by Mesel et al. [64]. The algorithms were developed in response to a desire to allow private practitioners, at a distance from the regional tertiary-care center, to manage the complex chemotherapy for their cancer patients, without routinely referring them to the central oncologists. Mesel et al. have described a "consultant-extender system" that enables the primary physician to treat patients with Hodgkin's Disease under the supervision of a regional specialist. Five oncologists developed a care protocol for the treatment of

Hodgkin's Disease, and this algorithm was placed on-line. Once patients had been entered in the study, their private physicians would prepare encounter forms at the time of each office visit. These forms would document pertinent interval history, physical findings, and lab data, as well as chemotherapy administered. The form would then be sent to the regional center where it was analyzed by the computer and a customized clinical algorithm was produced to assist the private physician with the management of that patient during the next appointment. Thus the computer program would take into account the ways in which the individual patient's disease might progress or improve and would prepare an appropriate clinical algorithm. This protocol was sent back to the physician in time for it to be available at the next office visit. The private practitioner was encouraged to call the regional specialist directly if the protocol seemed in some way inadequate or additional questions arose. The authors present data suggesting that their system was well-accepted by physicians and patients, and that excellent care was delivered. This is an interesting result in light of Grimm's experience [34]. Perhaps physicians were more accepting of the algorithmic approach in Mesel's case because it allowed them to perform tasks that they would previously not have been able to undertake at all. Retrospective review of cases that were treated at the referral center, but without the use of the protocols, showed a 16% rate of variance from the management guidelines specified in the algorithms; there was no such variance when the protocols were utilized directly. Thus algorithms may be effective tools for the administration of complex specialized therapy in circumstances such as those described.

2.3 Discussion of the Methodology

Although clinical algorithms are among the most widespread and accepted of the decision aids described in this article, the simplicity of their logic makes it clear why the technique cannot be effectively applied in most medical domains. Decision points in the algorithms are generally binary (i.e., a given sign or symptom is or is not present), and there tend to be many circumstances that can arise for which the user is advised to consult the supervising physician (or specialist). Thus the complex decision tasks are left to experts, and there is generally no formal algorithm for managing the case from that point on. It is precisely the simplicity of the algorithmic logic, and the supervising expert "escape valve", which has permitted many algorithms to be